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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Hermona Soreq, et al.
U.S. Serial No.	:	10/529,511 ✓
Filed	:	as §371 national stage of PCT/IL2003/000764, filed September 24, 2003
For	:	PARKINSON'S DISEASE SUSCEPTIBILITY HAPLOTYPE AS A TOOL FOR GENETIC SCREENING

1185 Avenue of the Americas
New York, New York 10036
March 17, 2006

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

In order to ensure compliance with applicants' duty of disclosure under 37 C.F.R. §1.56 and §1.97(a)-(d), applicants request that the following documents be considered and made of record in the above-identified application which is listed on Form PTO-1449, attached hereto as **Exhibit A:**

1. Abbott C. A., Mackness, M. I., Kumar, S., Olukoga, O., Gordon, C., Arrol, S., Bhatagar, D., Boulton, A. J. M., and Durrington, P. N. (1993) Relationship between serum butyrylcholinesterase activity, hypertriglyceridaemia and insulin sensitivity in diabetes mellitus. *Clin. Sci. (Lond)* 85: 77-81 **(Exhibit 1)**;

2. Adkins, S., Gan, K.N., Mody, M., and La Du, B. N. (1993) Molecular basis for the polymorphic forms of human serum paraoxonase/arylesterase: glutamine or arginine at position 191, for the respective A or B allozymes. *Am. J Hum. Genet.* 52: 598-608 **(Exhibit 2)**;

3. Akhmedova, S., Anisimov, S., Yakimovsky, A., and Schwartz, E. (1999) Gln → Arg 191 polymorphism of paraoxonase and Parkinson's disease. *Hum. Hered.* 49: 178-180 **(Exhibit 3)**;

4. Aminoff, M. J. (2001) Parkinson's disease and other extrapyramidal disorders. In: Braunwald, E., et al. (eds) Harrison's principles of internal medicine. McGraw Hill, pp. 2399-2406 **(Exhibit 4)**;

5. Bartels, C. F., Jensen, F. S., Lockridge, O., van der Spek, A. F., Rubinstein, H. M., Lubrano, T., and La Du, B. N. (1992) DNA mutation associated with the human butyrylcholinesterase K-variant and its linkage to the atypical variant mutation and other polymorphic sites. *Am. J. Hum. Genet.* 50: 1086-1103 **(Exhibit 5)**;

6. Betarbet, R., Sherer, T. B., MacKenzie, G., Garcia-Osuna, M., Panov, A. V., and Greenamyre, J. T. (2000) Chronic systemic pesticide exposure reproduces features of Parkinson's disease. *Nature Neurosci.* 3: 1301-1306 **(Exhibit 6)**;

7. Brindle, N., Song, Y., Rogaeva, E., Premkumar, S., Levesque, G., Yu, G., Ikeda, M., Nishimura, M., Paterson, A., Sorbi, S., Duara, R., Farrer, L., and St George-Hyslop, P. (1998) Analysis of the butyrylcholinesterase gene and nearby chromosome 3 markers in Alzheimer disease. *Hum. Mol. Genet.* 7: 933-935 **(Exhibit 7)**;

8. Brophy, V. H., Jampsa, R. L., Clendenning, J. B., McKinstry, L. A., Jarvik, G. P., and Furlong, C. E. (2001) Effects of 5' regulatory-region polymorphisms on paraoxonase-gene (PON1) expression. *Am. J. Hum. Genet.* 68: 1428-1436 **(Exhibit 8)**;

9. Brophy, V. H., Hastings, M. D., Clendenning, J. B., Richter, R. J., Jarvik, G. P., and Furlong, C. E. (2001) Polymorphisms in the human paraoxonase (PON1) promoter. *Pharmacogenetics* 11: 77-84 **(Exhibit 9)**;

10. Burkhardt, C., Kelly, J. P., Lim, Y. H., Filley, C. M., and Parker, W. D. Jr. (1993) Neuroleptic medications inhibit complex I of the electron transport chain. *Ann. Neurol*. 33: 512-517 **(Exhibit 10)**;

11. Cassarino, D. S., Fall, C. P., Swerdlow, R. H., Smith, T. S., Halvorsen, E. M., Miller, S. W., Parks, J. P., Parker, W. D. Jr., and Bennett, J. P. Jr. (1997) Elevated reactive oxygen species and antioxidant enzyme activities in animal and cellular models of Parkinson's disease. *Biochim. Biophys. Acta*, 1362: 77-86 **(Exhibit 11)**;

12. Costa, L. G., Cole, T. B., Jarvik, G. P., and Furlong, C. E. (2003) Functional genomic of the paraoxonase (PON1) polymorphisms: effects on pesticide sensitivity, cardiovascular disease, and drug metabolism. *Annu. Rev. Med*. 54: 371-392 **(Exhibit 12)**;

13. Costa, L. G., Richter, R. J., Murphy, S. D., Omenn, G. S., Motulsky, A. G., and Furlong, C. E. (1987) Species differences in serum paraoxonase correlate with sensitivity to paraoxon toxicity. In: Costa, L. G. (eds.) Toxicology of pesticides: experimental, clinical and regulatory perspectives. Springer-Verlag, Heidelberg, pp. 263-266 **(Exhibit 13)**;

14. Costa, L. G., Li, W. F., Richter, R. J., Shih, D. M., Lusis, A., and Furlong, C. E. (1999) The role of paraoxonase (PON1) in the detoxication of

organophosphates and its human polymorphism. *Chem. Biol. Interact.* 119-120: 429-438 **(Exhibit 14)**;

15. Dempster, A. P., Laird, N. M., and Rubin, D. B. (1977) Maximum Likelihood from Incomplete Data via the *EM* Algorithm. *J. Royal Statist. Soc. Ser. B. 39* **(Exhibit 15)**;

16. Furlong, C. E., Li, W. F., Costa, L. G., Richter, R. J., Shih, D. M., and Lusis, A. J. (1998) Genetically determined susceptibility to organophosphorus insecticides and nerve agents: developing a mouse model for the human PON1 polymorphism. *Neurotoxicology* 19: 645-650 **(Exhibit 16)**;

17. Goldsmith, J. R., Herishanu, Y., Abarbanel, J. M., and Weinbaum, Z. (1990) Clustering of Parkinson's Disease Points to Environmental Etiology. *Arch. Environ. Health* 45: 88-94 **(Exhibit 17)**;

18. Haley, R. W., Billecke, S., and La Du, B. N. (1999) Association of low PON1 type Q (type A) arylesterase activity with neurologic symptom complexes in Gulf War veterans. *Toxicol. Appl. Pharmacol.* 157: 227-233 **(Exhibit 18)**;

19. Herishanu, Y. O., Goldsmith, J. R., Abarbanel, J. M., and Weinbaum, Z. (1989) Clustering of Parkinson's Disease in Southern Israel. *Can. J. Neurol. Sci.* 16: 402-405 **(Exhibit 19)**;

20. Hodgson, E. and Lewy, P. E. (1996) Pesticides: An Important but Underused Model for the Environmental Health Sciences. *Environ. Health Perspect.* 104: 97-106 **(Exhibit 20)**;

21. Jenner, P. and Olanow, C. W. (1996) Oxidative stress and the pathogenesis of Parkinson's disease. *Neurology* 47(Suppl 3): S161-S170 **(Exhibit 21)**;

22. Kitada, T., Asakawa, S., Hattori, N., Matsumine, H., Yamamura, Y., Minoshima, S. Yokochi, M., Mizuno, Y., and Shimizu, N. (1998) Mutation in the *parkin* gene cause autosomal recessive juvenile parkinsonism. *Nature* 392: 605-608 **(Exhibit 22)**;

23. Kruger, R., Kuhn, W., Muller, T., Woitalla, D., Graeber, M., Kosel, S., Przuntek, H., Epplen, J. T., Schols, L., and Riess, O. (1998) Ala30Pro mutation in the gene encoding α-synuclein in Parkinson's disease. *Nat. Genet.* 18: 106-108 **(Exhibit 23)**;

24. Lang, A. E. and Lozano, A. M. (1998) Parkinson's Disease. First of Two Parts. *N. Engl. J. Med.* 339: 1044-1053 **(Exhibit 24)**;

25. Le Couteur, D. G., Muller, M., Yang, M. C., Mellick, G. D., and McLean, A. J. (2002) Age-environment and gene-environment interactions in the pathogenesis of Parkinson's disease. *Rev. Environ. Health* 17: 51-64 **(Exhibit 25)**;

26. Lehmann, D. J., Nagy, Z., Litchfield, S., Borja, M. C., and Smith, A. D. (2000) Association of butyrylcholinesterase K variant with cholinesterase-positive neuritic plaques in the temporal cortex in late-onset Alzheimer's disease. *Hum. Genet.* 106: 447-452 **(Exhibit 26)**;

27. Lehmann, D. J., Johnston, C., and Smith A. D. (1997) Synergy between the genes for butyrylcholinesterase K

variant and apolipoprotein E4 in late-onset confirmed Alzheimer's disease. *Hum. Mol. Genet.* 6: 1933-1936 **(Exhibit 27)**;

28. Lockridge, O. and Masson, P. (2000) Pesticides and Susceptible Populations: People With Butyrylcholinesterase Genetic Variants May Be At Risk. Genetic *Neurotoxicology* 21: 113-126 **(Exhibit 28)**;

29. Loewenstein-Lichtenstein, Y., Schwarz, M., Glick, D., Norgaard-Pedersen, B., Zakut, H., and Soreq, H. (1995) Genetic predisposition to adverse consequences of anti-cholinesterases in 'atypical' BCHE carriers. *Nat. Med.* 1: 1225-1226 **(Exhibit 29)**;

30. Lucking, C. B., Durr, A., Bonifati, V., Vaughan, J., De Michele, G., Gasser, T., Harhangi, B. S., Meco, G., Denefle, P., Wood, N. W., Agid, Y., and Brice, A. (2000) Association between early-onset Parkinson's disease and mutations in the parkin gene. French Parkinson's Disease Genetics Study Group. *N. Engl. J. Med.* 342: 1560-1567 **(Exhibit 30)**;

31. Mackness, B., Durrington, P. N., and Mackness, M. I. (1998) Human Serum Paraoxonase. *Gen. Pharmacol.* 31: 329-336 **(Exhibit 31)**;

32. Masson, P., Josse, D., Lockridge, O., Viguie, N., Taupin, C., and Buhler, C. (1998) Enzymes hydrolyzing organophosphates as potential catalytic scavengers against organophosphate poisoning. *J. Physiol. (Paris)* 92: 357-362 **(Exhibit 32)**;

33. Menegon, A., Board, P. G., Blackburn, A. C., Mellick, G. D., and Le Couteur, D. G. (1998) Parkinson's disease, pesticides, and glutathione transferase

polymorphisms. *Lancet* 352: 1344-1346 **(Exhibit 33)**;

34. Nassar, B. A., Dunn, J., Title, L. M., O'Neill, B. J., Kirkland, S. A., Zayed, E., Bata, I. R., Cantrill, R. C., Johnstone, J., Dempsey, G. I., Tan, M. H., Breckenridge, W. C., and Johnstone, D. E. (1999) Relation of genetic polymorphisms of apolipoprotein E, angiotensin converting enzyme, apolipoprotein B-100, and glycoprotein IIIa and early-onset coronary heart disease. *Clin. Biochem.* 32: 275-282 **(Exhibit 34)**;

35. Nassar, B. A., Darvesh, S., Bevin, L. D., Rockwood, K., Kirkland, S. A., O'Neill, B. J., Bata, I. R., Johnstone, D. E., and Title, L. M. (2002) Relation between butyrylcholinesterase K variant, paraoxonase 1 (PON1) Q and R and apolipoprotein E ∈4 genes in early-onset coronary artery disease. *Clin. Biochem.* 5: 205-209 **(Exhibit 35)**;

36. Parker, W. D. and Swerdlow, R. H. (1998) Mitochondrial dysfunction in idiopathic Parkinson disease. *Am. J. Hum. Genet.* 62: 758-762 **(Exhibit 36)**;

37. Polymeropoulos, M. H., Lavedan, C., Leroy, E., Ide, S. E., Dehejia, A., Dutra, A., Pike, B., Root, H., Rubenstein, J., Boyer, R., Stenroos, E. S., Chandrasekharappa, S., Athanassiadou, A., Papapetropoulos, T., Johnson, W. G., Lazzarini, A. M., Duvoisin, R. C., Di Iorio, G., Golbe, L. I., and Nussbaum, R. L. (1997) Mutation in the α-synuckein gene identified in families with Parkinson's disease. *Science* 276: 2045-2047 **(Exhibit 37)**;

38. Premkumar, D. R., Cohen, D. L., Hedera, P., Friedland, R. P., and Kalaria, R. N. (1996) Apolipoprotein E-∈4

alleles in cerebral amyloid angiopathy and cerebrovascular pathology associated with Alzheimer's disease. *Am. J. Pathol.* 148: 2083-2095 **(Exhibit 38)**;

39. Spillantini, M. G., Schmidt, M. L., Lee, V. M.-Y., Trojanowski, J. Q., Jakes, R., and Goedert, M. (1997) α-Synuclein in Lewy Bodies. *Nature* 388: 839-40 **(Exhibit 39)**;

40. Suehiro, T., Nakamura, T., Inoue, M., Shiinoki, T., Ikeda, Y., Kumon, Y., Shindo, M., Tanaka, H., and Hashimoto, K. (2000) A polymorphism upstream from the human paraoxonase (PON1) gene and its association with PON1 expression. *Atherosclerosis* 150: 295-298 **(Exhibit 40)**;

41. Sveinbjörnsdóttir, S., Hicks, A. A., Jónsson, T., Pétursson, H., Guðmundsson, G., Grigge, M. L., Kong, A., Gulcher, J. R., and Stefánsson, K. (2000) Familial Aggegation of Parkinson's Disease in Iceland. *N. Engl. J. Med.* 343: 1765-1770 **(Exhibit 41)**;

42. Tanner, C. M., Ottman, R., Ellenberg, J. H., Goldman, S. M., Mayeux, R., Chan, P., and Langston, J. W. (1997) Parkinson's Disease (PD) Concordance in Elderly Male Monozygotic (MZ) and Dizygotic (DZ) Twins. *Neurology* 48(Suppl): A333 **(Exhibit 42)**;

43. Taylor, M. C., Le Couteur, D. G., Mellick, G. D., and Board, P. G. (2000) Paraoxonase polymorphisms, pesticide exposure and Parkinson's disease in a Caucasian population. *J. Neural Transm.* 107: 979-983 **(Exhibit 43)**;

44. Vays, I., Heikkila, R. E., and Nicklas, W. J. (1986)

Studies on the neurotoxicity of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine: inhibition of NAD-linked substrate oxidation by its metabolite, 1-methyl-4-phenylpyridinium. *J. Neurochem.* 46: 1501-1507 **(Exhibit 44)**;

45. Vingerhoets, F. J. G., Snow, B. J., Tetrud, J. W., Langston, J. W., Schulzer, M., and Calne, D. B. (1994) Positron emission tomographic evidence for progression of human MPTP-induced dopaminergic lesions. *Ann. Neurol.* 36: 765-770 **(Exhibit 45)**;

46. Wang, J. and Liu, Z. (2000) No association between paraoxonase 1 (PON1) gene polymorphisms and susceptibility to Parkinson's disease in a Chinese population. *Mov. Disord.* 15: 1265-1267 **(Exhibit 46)**;

47. Wooten, G. F., Currie, L. J., Bennett, J. P., Harrison, M. B., Trugman, J. M., and Parker, W. D. Jr. (1997) Maternal inheritance in Parkinson's disease. *Ann. Neurol.* 41: 265-268 **(Exhibit 47)**;

48. Poewe, W. H. and Wenning, G. K. (1996) The natural history of Parkinson's disease. *Neurology* 47(Suppl 3): S146-S152 **(Exhibit 48)**;

49. International Preliminary Examination Report issued by the International Preliminary Examination Authority (IPEA/EP) on December 27, 2004 in connection with International Application No. PCT/IL2003/000764 **(Exhibit 49)**;

50. International Search Report issued by the International Searching Authority (ISA/EP) on April 6, 2004 in connection with International Application No. PCT/IL2003/000764 **(Exhibit 50)**;

51. Akhmedova, S. N., Yakimovsky, A. K., and Schwartz, E. I. (2001) Paraoxonase 1 Met-Leu 54 Polymorphism Is Associated With Parkinson's Disease. *J. Neurol. Sci.* 184: 179-182 **(Exhibit 51)**;

52. Shapira, M., Tur-Kaspa, I., Bosgraaf, L., Livni, N., Grant, A. D., Grisaru, D., Korner, M., Ebstein, R. P., and Soreq, H. (2000) A transcription-activating polymorphism in the *ACHE* promoter associated with acute sensitivity to anti-acetylcholinesterases. *Hum. Mol. Genet.* 9: 1273-1281 **(Exhibit 52)**;

53. Kondo, I. and Yamamoto, M. (1998) Genetic Polymorphism Of Paraoxonase 1 (PON1) And Susceptibility To Parkinson's Disease. *Brain Res.*, 806: 271-273 **(Exhibit 53)**;

54. Bartels, C. F., Zelinski, T., and Lockridge, O. (1993) Mutation at Codon 322 in the Human Acetylcholinesterase (ACHE) Gene Accounts for YT Blood Group Polymorphism. *Amer. J. Hum. Genet.* 52: 928-936 **(Exhibit 54)**;

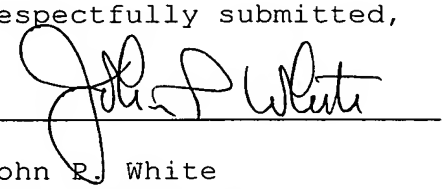
55. Carmine, A., Buervenich, S., Sydow, O., Anvret, M., and Olson, L. (2002) Further Evidence for an Association of the Paraoxonase 1 (PON1) Met-54 Allele with Parkinson's Disease. *Movement Disord.* 17: 764-766 **(Exhibit 55)**; and

56. Kaufer, D. and Soreq, H. (1999) Tracking Cholinergic Pathways from Psychological and Chemical Stressors to Variable Neurodeterioration Paradigms. *Curr. Opin. Neurol.* 12: 739-743 **(Exhibit 56)**.

Copies of documents numbers 1-56 are attached hereto as **Exhibits 1-56**, respectively.

No fee is deemed necessary in connection with the filing of this Information Disclosure Statement. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
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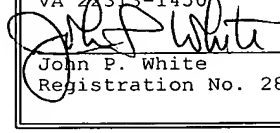

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John P. White Date
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 1 of 6

Complete if Known	
Application Number	10/529,511
Filing Date	§371 of PCT/IL2003/000764
First Named Inventor	Hermona Soreq
Art Unit	
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Attorney Docket Number	74136/JPW/JW

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	1	Abbott C. A., Mackness, M. I., Kumar, S., Olukoga, O., Gordon, C., Arrol, S., Bhatagar, D., Boulton, A. J. M., and Durrington, P. N. (1993) Relationship between serum butyrylcholinesterase activity, hypertriglyceridaemia and insulin sensitivity in diabetes mellitus. *Clin. Sci. (Lond)* 85: 77-81	
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Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

1 Applicant's unique citation designation number (optional). 2 Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Applicants: Hermona Soreq, et al.
U.S. Serial No. 10/529,511
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Exhibit A

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	11	Cassarino, D. S., Fall, C. P., Swerdlow, R. H., Smith, T. S., Halvorsen, E. M., Miller, S. W., Parks, J. P., Parker, W. D. Jr., and Bennett, J. P. Jr. (1997) Elevated reactive oxygen species and antioxidant enzyme activities in animal and cellular models of Parkinson's disease. *Biochim. Biophys. Acta*, 1362: 77-86	
	12	Costa, L. G., Cole, T. B., Jarvik, G. P., and Furlong, C. E. (2003) Functional genomic of the paraoxonase (PON1) polymorphisms: effects on pesticide sensitivity, cardiovascular disease, and drug metabolism. *Annu. Rev. Med.* 54: 371-392	
	13	Costa, L. G., Richter, R. J., Murphy, S. D., Omenn, G. S., Motulsky, A. G., and Furlong, C. E. (1987) Species differences in serum paraoxonase correlate with sensitivity to paraoxon toxicity. In: Costa, L. G. (eds.) Toxicology of pesticides: experimental, clinical and regulatory perspectives. Springer-Verlag, Heidelberg, pp. 263-266	
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	15	Dempster, A. P., Laird, N. M., and Rubin, D. B. (1977) Maximum Likelihood from Incomplete Data via the EM Algorithm. *J. Royal Statist. Soc. Ser. B.* 39	
	16	Furlong, C. E., Li, W. F., Costa, L. G., Richter, R. J., Shih, D. M., and Lusis, A. J. (1998) Genetically determined susceptibility to organophosphorus insecticides and nerve agents: developing a mouse model for the human PON1 polymorphism. *Neurotoxicology* 19: 645-650	
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	19	Herishanu, Y. O., Goldsmith, J. R., Abarbanel, J. M., and Weinbaum, Z. (1989) Clustering of Parkinson's Disease in Southern Israel. *Can. J. Neurol. Sci.* 16: 402-405	
	20	Hodgson, E. and Lewy, P. E. (1996) Pesticides: An Important but Underused Model for the Environmental Health Sciences. Environ. *Health Perspect.* 104: 97-106	

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Sheet 3 of 6

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Application Number	10/529,511
Filing Date	§371 of PCT/IL2003/000764
First Named Inventor	Hermona Soreq
Art Unit	
Examiner Name	
Attorney Docket Number	74136/JPW/JW

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	21	Jenner, P. and Olanow, C. W. (1996) Oxidative stress and the pathogenesis of Parkinson's disease. *Neurology* 47(Suppl 3): S161-S170	
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Sheet 4 of 6

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First Named Inventor	Hermona Soreq
Art Unit	
Examiner Name	
Attorney Docket Number	74136/JPW/JW

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	31	Mackness, B., Durrington, P. N., and Mackness, M. I. (1998) Human Serum Paraoxonase. *Gen. Pharmacol.* 31: 329-336	
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	41	Sveinbjörnsdóttir, S., Hicks, A. A., Jónsson, T., Pétursson, H., Guðmundsson, G., Grigge, M. L., Kong, A., Gulcher, J. R., and Stefánsson, K. (2000) Familial Aggegation of Parkinson's Disease in Iceland. *N. Engl. J. Med.* 343: 1765-1770	
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	52	Shapira, M., Tur-Kaspa, I., Bosgraaf, L., Livni, N., Grant, A. D., Grisaru, D., Korner, M., Ebstein, R. P., and Soreq, H. (2000) A transcription-activating polymorphism in the ACHE promoter associated with acute sensitivity to anti-acetylcholinesterases. *Hum. Mol. Genet.* 9: 1273-1281	
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